

PROMOTION AND TENURE
Assistant Professor to Associate Professor
Area of Excellence — Research
School of Medicine
2008-09

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SIGNIFICANT UPDATES TO DOSSIER:

I am submitting additional information to my promotion and tenure dossier in the areas of Research and Teaching. Significantly, since submission of the dossier, I have received notification of the following:

I. Research:

- a. The clinical trial on the use of telomerase inhibitors for breast cancer therapy, as described in the "Candidate's Statement," is now active and has enrolled three patients for its first dose level as of August 8, 2008. Study # CPA14010: "A Phase I/II Study of GRN163L in Combination with Paclitaxel and Bevacizumab in Patients with Locally Recurrent or Metastatic Breast Cancer."
- b. A second, correlative clinical trial entitled "A Study of Telomerase Inhibition in Circulating Tumor Cells after Treatment with GRN163L in the Geron-sponsored CPA14010 Study," on which I am the *Principal Investigator*, was activated on August 7, 2008. The activation notice for this study is attached.
- c. Related to this study, **funding was awarded** from the national Breast Cancer Research Foundation (BCRF) in the amount of \$250,000 per year (\$208,333 direct, yr1) for the proposal entitled "A Study of Telomerase Inhibition in Circulating Tumor Cells after Treatment with GRN163L." This grant was awarded for one year beginning October 1, 2008 and is renewable every year. My role on this grant will be to lead the investigation on the effects of telomerase inhibition (via the GRN163L agent) on circulating tumor cell numbers and activity in breast cancer patients from the CPA14010 trial. This study will be the first to analyze the effects of telomerase inhibitors on circulating tumor cells in breast cancer patients. As the co-investigator for this study, I receive 10% support for my salary, technician support (50% effort) and ~\$40,000 in supplies for my laboratory per year. The principal investigator and collaborator, Kathy Miller, M.D. (IU School of Medicine), is in charge of the parent clinical trial (CPA14010). A copy of the BCRF grant award notice is attached.
- d. The manuscript entitled "Premature Senescence of Cord-Blood Derived Endothelial Progenitor Cells Induced by Tumor Necrosis Factor-alpha and Oxidative Stress" (Zhang, Herbert et al.) has been accepted pending minor revisions to the *FASEB Journal* (Impact factor 6.791). A copy of the letter from the Editor is attached.

II. Teaching:

- a. As evidence of teaching outcomes, my graduate student, Erin Goldblatt, has accepted a position as an NIH T32 post-doctoral trainee in "Translational Research in Cancer Genomic Medicine" with Dr. Wen-Hwa Lee, Chair of the Department of Biological Chemistry at The University of California-Irvine. Dr. Lee is the Donald Bren Professor of Biomedicine and is renowned for identifying a tumor-suppressor gene (*Rb*) that plays a vital role in the cellular battle against cancer. Dr. Lee is an expert on DNA repair genes and cancer. Ms. Goldblatt's postdoctoral fellowship will begin in November, 2008. A copy of her offer letter is attached.
- b. I have also been accepted as a mentor to an undergraduate through IUPUI's Life-Health Science Internship program for the 2008-2009 school year. A copy of that notification is attached.

Note: A copy of this update and the supporting material is included in the Appendix.

SIGNIFICANT UPDATES TO DOSSIER:

I am submitting additional information to my promotion and tenure dossier in the area of Research. Significantly, since submission of the dossier and previous update on August 12, 2008, I have received notification of the following:

- **Research:**

The manuscript entitled “Lipid-conjugated telomerase antagonists sensitize resistant HER2-positive breast cancer cells to trastuzumab” (by Goldblatt EM, Erickson PA, Gentry ER, Gryaznov SM, and Herbert B-S) has been accepted for publication within the journal *Breast Cancer Research and Treatment* (Impact factor 4.453; the highest impact factor for a breast cancer-specific journal). Erin Goldblatt, a PhD graduate student within my laboratory is first author on this paper and I am the corresponding author. Co-author Priscilla Erickson was an undergraduate student researcher within my laboratory. This is the first report of a telomerase inhibitor, currently in clinical trials, inhibiting cell growth and restoring sensitivity to therapy in Herceptin™ resistant breast cancer cells.

CANDIDATE'S STATEMENT

After completing my postdoctoral research fellowship, I joined the faculty of the Department of Medical and Molecular Genetics at Indiana University School of Medicine (IUSM) in September 2003. I was recruited to this institution for my work on telomerase and a potential new breast cancer therapeutic agent that could be moved to a clinical trial at IUSM. In addition, I was attracted to the idea of continuing my academic career at IUSM on the IUPUI campus because of its strong clinical and translational research achievements, particularly in breast cancer, and its recognition as a leader in education. Since joining the faculty, the focus of my academic career has been in the area of research. While in rank, I have produced thirteen research papers in peer-reviewed journals, in addition to three invited review articles and one book chapter, of which I am first or senior/corresponding author on eight of these publications/ book chapter. Furthermore, I have received national and international recognition as an Assistant Professor of Medical and Molecular Genetics and have been continuously funded for my research efforts. My research efforts have also resulted in sustained and productive collaborations with my colleagues. I have provided significant contributions for translational cancer research as a member of the Indiana University Melvin and Bren Simon Cancer Center (IUSCC). In addition to my research activities, I have also been an active participant in the IUSM's/IUPUI's teaching and service missions.

Research: Area of Excellence

The goals of my research are to understand the mechanisms of carcinogenesis in order to develop novel therapeutic and preventative agents for the improved treatment of cancer. *My particular research focus* over the past few years has been on therapeutic approaches for breast cancer by targeting telomeres and telomerase. Telomeres are the terminal DNA sequences at the ends of chromosomes which are crucial for protecting chromosome ends from fusions and being recognized as damaged DNA. Telomerase is a large ribonucleoprotein complex responsible for replicating and maintaining telomeric DNA. My initial work on telomeres and telomerase began while I was a postdoctoral fellow in Jerry Shay's and Woodring Wright's aging and cancer laboratory at UT-Southwestern Medical Center at Dallas. It was there that I championed the work on short oligonucleotide inhibitors of telomerase as novel cancer therapeutic agents. Unlike the most normal cells, the vast majority (>90%) of human cancer cells express active telomerase. This difference makes telomerase inhibition an attractive, non-toxic anti-cancer therapeutic target. I was one of the first to demonstrate that short oligonucleotides could inhibit telomerase activity, shorten telomeres, and significantly reduce human cancer cell growth (Herbert et al., *PNAS* 1999, *Oncogene* 2002). Based on these initial observations, my goal was to continue these studies as an independent investigator focusing on breast cancer. This work has set the stage for significant pre-clinical discoveries from my laboratory on the effects of telomerase inhibition in breast cancer cells and the combination of telomerase inhibitors with other treatments as described below. My studies on targeting telomerase for breast cancer therapy have been funded continuously since 2004 by various mechanisms such as the Mary Kay Ash Foundation, American Cancer Society junior investigator award, Phi Beta Psi National Society (one of six recipients nationwide), and the Showalter Trust, with the development/resubmission of a National Institute of Health (NIH) R01 grant proposal.

The first task to bringing telomerase inhibitors to the clinic was to test modifications of the oligonucleotides that allowed for potent and stable inhibition of telomerase in cancer cells. As an Assistant Professor at IUSM, I was the first to demonstrate that a lipid modification of a specific telomerase antagonist, GRN163L, synthesized in collaboration with a research chemist at the Geron Corporation, allowed for the efficient inhibition of telomerase in breast cancer cells (*Oncogene* 2005). More importantly, my laboratory was the first to show that GRN163L significantly limited breast tumor growth and metastases to the lung in a large animal study that models a clinical situation for human breast cancer (*Clin Cancer Res.* 2006).

The next logical step towards bringing telomerase inhibitors to the clinic was to independently show that the telomerase antagonist, GRN163L, can be used in combination with other therapeutic regimens for breast

cancer. This work has been championed by my Ph.D. graduate student who has worked rigorously in the lab and is interested in translational breast cancer research. First, in collaboration with radiation biologist Dr. Marc Mendonca (Assoc. Professor, IUSM), we demonstrated that breast cancer cells with shortened telomeres due to growth in the presence of GRN163L were more susceptible to effects of irradiation than their control counterparts. Importantly, my laboratory confirmed these results *in vivo*, with a significant decrease in tumor growth in mice exposed to GRN163L and irradiation (*Intl J Rad Oncology*, 2007). This work demonstrates a potential adjuvant treatment option that may improve the therapeutic index by enhancing the radiation sensitivity of cancers. Second, my laboratory has made the significant observation that GRN163L can inhibit telomerase and cell growth in breast cancer cells that acquired resistance to Herceptin (Goldblatt et al., submitted). Herceptin is a monoclonal antibody targeting HER2 which is amplified in ~20% of breast cancers. Unfortunately, a large proportion of HER2 breast cancer patients develop resistance to Herceptin; therefore, improved therapeutic regimens are needed. To this end, we showed that GRN163L altered HER2 signaling and was not only synergistic with Herceptin in Herceptin-sensitive breast cancer cells, but GRN163L inhibited growth and restored sensitivity to Herceptin in Herceptin-resistant breast cancer cells. These results have been submitted as a late-breaking abstract for the American Association for Cancer Research annual meeting in 2008. Finally, my laboratory is also preparing to submit a manuscript on our findings demonstrating that GRN163L can alter cellular structural elements, permitting GRN163L to synergize with the chemotherapeutic paclitaxel in breast cancer cells. These observations on telomerase inhibitors have *led to the development of a proposed 5-year NIH R01 grant application to examine* the mechanisms of telomerase inhibitors in order to design rational combination therapy for breast cancer.

Metastasis, tumor relapse, and drug resistance remain as major obstacles in the treatment of breast cancer. Cancer stem cells have been proposed as the source of these obstacles. Stem cells most likely regulate telomerase activity to maintain their indefinite proliferative potential when stimulated. Therefore, to approach this problem, in the lab, we are investigating the role of telomerase in breast cancer stem/progenitor cells with the potential to target these cells using telomerase inhibitor oligonucleotides or small molecules. I have been privileged to be funded for this study by the Mary Kay Ash Foundation for women's cancer research (recognized by IUSM as a prestigious external grant; <http://medicine.iu.edu/body.cfm?id=1261>). It is anticipated that my independent investigations on the role of telomerase in breast cancer stem cells over the next 2-4 years will *further the efforts* in the eradication of breast cancer recurrence, resistance, and metastasis.

One of the most rewarding accomplishments and culmination of my research on telomerase inhibition as an Assistant Professor at IUSM is that I have successfully initiated a *multicenter clinical trial*, in collaboration with IU clinical trials director and breast cancer therapeutics expert Kathy Miller, M.D., to determine whether GRN163L is an effective treatment when given in combination with paclitaxel/Avastin in patients with locally recurrent or metastatic breast cancer (Geron Corporation-sponsored; PI: Miller, co-PI: Herbert). I am also the *Principal Investigator* on a correlative study to investigate the inhibition of telomerase in circulating tumor cells from these patients as a surrogate marker and proof-of-concept that the agent is hitting its target. This work will utilize methods from a *Nature Protocols* paper from my lab (Herbert et al., 2006) of which reprints have been requested by many of my peers. This study represents a significant breakthrough in breast cancer research and has been viewed with considerable interest and excitement by my colleagues here in the IUSM Breast Cancer Program. Most gratifying, therefore, is that not only have I increased our understanding of telomerase inhibitors, but I have applied this knowledge towards their use in the clinic to prolong patients' lives.

Extending from the above investigations on short oligonucleotide-based telomerase inhibitors, my laboratory is investigating other potential negative regulators of telomerase such as molecules that modify the DNA/chromatin, DNA methylation, and microRNAs (currently funded by the US Department of Defense (DOD), in which only 10% of proposals were funded). This DOD study aims to address a new model proposing that epigenetic regulators, present as microRNAs that inhibit telomerase, are expressed in normal cells, but are

no longer expressed in cancer cells. *Over the next 3-5 years*, I aim to: 1) correlate the expression of telomerase activity with the predicted telomerase microRNAs (that negatively regulate telomerase) in normal and cancer cells; 2) determine the effects of these microRNAs on telomerase activity and accessibility (via telomere-associated proteins) in cancer cells; and, 3) test the hypothesis that inactivation of telomerase by microRNAs inhibits the growth of cancer cells. This study has led to a collaboration with a microRNA and cancer hypoxia expert, Dr. Mircea Ivan (Tufts University), which should enhance my efforts. The *long-term goal* is to collaborate with IU Chemists to determine the optimal delivery of microRNA oligos as novel anti-cancer therapy reagents. Importantly, this research project has been mapped as part of the IU Translational Research Acceleration Collaboration (ITRAC) and my map was recently selected by the senior leaders of the cancer center to be presented during the National Cancer Institute's site visit in January 2008 (for competitive center renewal) since my research was successfully funded by the DOD.

More recently, complimentary efforts in my laboratory have been the screening of novel therapeutics to target factors that influence breast carcinogenesis, which is currently funded by the NIH. These studies should ultimately provide constructive insight into which agents should be developed for inclusion in clinical prevention trials. Based on publications that I initiated during my postdoctoral career demonstrating the inhibition of the spontaneous immortalization of breast epithelial cells by chemopreventive agents, I was awarded independent funding by the NIH-sponsored National Cancer Institute (NCI) Division of Chemoprevention to use high-throughput screening of natural/dietary and synthetic agents for novel breast cancer treatment and chemoprevention. This award has been regularly peer-reviewed (quarterly reports to the NCI program directors) for continued funding with the potential for competitive renewal. For this study, I have developed an *in vitro* system of transformed mammary epithelial cells that can represent different stages of breast cancer progression (Gentry et al., submitted). These tumorigenic mammary epithelial cells were derived from women who did not have breast cancer as well as patients who had inherited mutations in genes that predisposed them to breast cancer (e.g., Li-Fraumeni syndrome/*TP53*, *BRCA1*, or *BRCA2*). Not only do these cell lines provide useful tools for further studies on breast carcinogenesis in my laboratory, these cell lines have also been valuable to many collaborators who are members of the cancer center (e.g., Malkas, Herbert et al., *PNAS* 2006). Moreover, in collaboration with Dr. Brenda Grimes (Asst. Professor of Med. and Mol. Genetics, IUSM), an expert in cytogenetics and chromatin modification, we are utilizing these breast epithelial cell lines generated from my lab to dissect chromosomal changes during genomic instability and breast carcinogenesis. *Further studies over the next five to ten years* in my lab are aimed at elucidating the mechanisms by which these agents contribute to the epigenetic regulation of genes (including telomerase regulation by microRNAs as above) involved in breast cancer cell growth and survival. Understanding this phenomenon in cancer is a current roadmap goal of the NIH; therefore, the data and resources within my laboratory will be used to develop *future extramural grant applications (NIH R01/R03)*. Integrating teaching efforts with research, I have had students and fellows actively participating in these investigations on agents to target carcinogenesis in inherited and spontaneous breast cancers which have resulted in scientific abstracts submitted by the students.

In addition to the significant works that stem from my lab, I have developed strong, interdisciplinary collaborations with other colleagues within IUSM and the Indiana University Simon Cancer Center (IUSCC), particularly with members of the Breast Cancer Program. Published outcomes from these collaborative projects (e.g., with Drs. David Gilley and Jalees Rehman, IUSM) are based on my expertise in telomeres/telomerase, senescence, and my development of cell lines representing different stages of breast cancer progression. One significant collaboration has been with Drs. Linda Malkas (Professor of Medicine, IUSM; co-leader of the Breast Cancer Program, IUSCC) and Robert Hickey (Assoc. Professor of Medicine, IUSM), experts in DNA replication and development of new biomarkers for cancer. With two key figures using my unique cell lines, a joint research paper with Drs. Malkas and Hickey on the role of a cancer-specific isoform of PCNA in breast cancer cell progression was published in *PNAS* in 2006. Furthermore, my collaboration with Dr. Malkas resulted in an NIH-R01 award. This long-term collaboration has resulted in the expansion of my research

efforts and the *development of future aims* such as the relationship between telomerase and human DNA replication as well as the impact of cellular aging/dietary agents on DNA replication fidelity in breast tissue. An anticipated outcome is the continued advancement in the understanding of genomic integrity in aging and cancer and potential therapy.

Since arriving in the fall 2003, my research efforts have resulted in nearly \$1 million in internal and external funding on which I am the Principal Investigator, with another ~\$2 million proposed. I have been continuously funded and I typically have 1-3 research proposals pending at any one time. In recognition of my expertise in telomerase inhibitors, I have submitted a book chapter with my Ph.D. graduate student. My *future goals* are to continue to target crucial factors that affect breast carcinogenesis, such as telomerase, in order to develop rational combinations with other breast cancer therapeutic regimens for clinical trials. These goals are part of my ITRAC research project map and external funding proposal submissions to federal agencies. These studies also have important implications for understanding how telomerase may be turned on which can aid in tissue or stem/progenitor cell regeneration. As telomerase is thought to play a role in the replicative potential of stem cells, it is important to understand how telomerase is regulated. Therefore, my vision of my research efforts in the activation of telomerase by natural or synthetic agents represents a tool for regenerative medicine, whereas its inhibition is currently being developed for breast cancer clinical trials.

Teaching

One of the benefits of being at an academic research institution is participating in the efforts of teaching as well as research. Teaching can encompass classroom lecturing, workshops, and mentoring. My main teaching philosophies are to lead by example, teach with enthusiasm, and to ensure my entire audience understands the topic with "take home lessons." My teaching responsibilities so far have been focused on providing lectures on telomeres/telomerase to the departmental courses as well as mentoring graduate students in the laboratory or on Ph.D./M.S. thesis committees. As evidence of my quality of teaching, I received excellent student evaluations for all my didactic teaching lectures and I have enjoyed seeing students come back to say they learned so much from their experiences in my class, laboratory, or interaction on committees.

As part of my didactic teaching efforts on campus, I have had the pleasure to routinely lecture on telomeres/telomerase to the Department of Medical and Molecular Genetics graduate level courses and the G852 Concepts in Cancer Biology course. I am also a Co-Course Director for a new cancer genetics course for the IUSM graduate students (G724: Molecular Cancer Genetics). I began development of this course in 2005 as a Q640: Special Topics in Genetics course because I felt the genetic aspect of cancer via student-led discussions on prominent papers had been lacking within the school's graduate program. I have fulfilled this need as well as providing an opportunity for my departmental faculty to lecture on their research. G724 is now a part of the IUSM graduate curriculum and is anticipated to be a part of the IU Cancer Biology Training Program. I have also worked with the IUPUI Office of Professional Development's Center for Teaching and Learning to monitor my teaching quality and *continued development* of this new course for future offerings.

Most of my efforts and contact hours in teaching include student mentoring, of which I find most rewarding. Over the past four years, I have mentored fifteen future junior scientists/physicians on the importance of research excellence through summer research programs, NIH training grants, and graduate student committees. An integral part of my teaching is incorporating student learning in my research laboratory by developing tangible research projects and working one-on-one with the students. As a result, most of the students that I have mentored have achieved co-authorships or first authorships on manuscripts or abstracts from my laboratory. For example, two of my students (an NIH R25 Bridges to Doctorate M.S. minority student and my Ph.D. student) have won awards for their abstracts at scientific symposiums. Of significant note, I am currently a Ph.D. advisor to Ms. Erin Goldblatt, a fourth year graduate student in the lab, who was a recipient of an IUSM Translational Research Fellowship to support her pre-clinical research focused on the upcoming breast cancer clinical trial using telomerase inhibitors. Erin is also currently a co-author or first-author on at least five publications from my laboratory including a book chapter on telomerase inhibitors. Erin represents a significant

achievement of my first graduate mentoring experience and it is expected that she will be able to graduate with her Ph.D. in 2008 and continue on for her postdoctoral studies in translational breast cancer research. *Future goals* in teaching include continuing to provide excellent mentorship to future scientists in the classroom or laboratory (including the IUPUI Life-Health Sciences Internships for undergraduates), and eventually take on a leadership role in graduate advising or summer research programs.

Service

I believe that an integral part of being a member of the faculty at an academic research institution is the sense of community through academic citizenship. I felt it important to serve on committees at the departmental, school, and campus/institutional level to enhance the University's missions as well as my own research. It has also been an honor to be elected by the faculty as a member of the IUSM Faculty Community Relations Committee to represent the University at community functions. As an example of how my service also fulfills other academic missions, I have served on the Departmental Graduate Student Admissions Committee as well as an interviewer for the past two years for the IUSM graduate student admissions in order to recruit top students to the school and our department. I have served on seven Ph.D./M.S. student thesis committees. As a local service to my discipline, I serve as a peer-reviewer for the IUSCC internal grant proposal submissions and on the Institutional Biosafety Committee. Being the speaker coordinator for the IUSCC Breast Cancer Research Program provides me the opportunity to meet respected breast cancer researchers. *In the future*, I will continue to strive to be an active academic citizen for this University by increasing my leadership roles, while promoting continued excellence in research and teaching at this institution.

As part of my professional service to my discipline and as evidence of national or international recognition for my research contributions, I have been asked to participate in peer review of research grant proposals, speak at national/international research conferences and seminar series, and chair sessions at conferences. Participation in peer review, particularly of grant proposals, is one of the most respected accolades to achieve for a researcher. Of significance, I have been privileged as an Assistant Professor to have been invited to participate on three national grant review committees (e.g., DOD) and one international grant review based on my expertise on telomerase and breast cancer experimental therapeutics. In addition, I serve as an *ad hoc* peer reviewer for several scientific journals including the American Association for Cancer Research (AACR) society journals, the main society for my field of cancer research. Furthermore, I have been invited to give oral presentations on my independent research at the American Society of Cell Biology meeting (San Francisco, 2003) and at the British Association for Cancer Research Telomerase and Cancer Stem Cells conference (York, UK, 2007). *Future goals* are to continue providing excellent service to my discipline by participating in peer review and gaining leadership roles in my professional organizations. Continued participation in these activities will allow for further feedback/recognition of my work and opportunity for research collaborations with my peers.

Summary

In summary, my accomplishments in telomerase research have resulted in the establishment of an independent, productive research laboratory that has set the stage for continued investigations for targeting factors that influence breast carcinogenesis for improved therapy. My research efforts on telomerase inhibition in breast cancer have resulted in significant funding with submissions for extramural funding to cover the next five years. More significantly, my research on telomerase inhibitors has resulted in a clinical trial for breast cancer that I have brought to IUSM. I have been an active and well-rounded scholar at IUSM/IUPUI as evidenced by collaborative research/grants, peer-reviewed creative activities and papers, grant submissions, successful teaching/mentoring, and service to the campus. My future plans are to continue to seek federal extramural funding to further elucidate the mechanistic basis of inhibition of telomerase and other genes involved in cancer progression which should result in improved design of new therapeutic agents and cancer patient survival. Furthermore, I will continue to seek opportunities to integrate my research expertise and enthusiasm into the missions of teaching as well as service to my discipline, University, and community.

1. Research and Creative Activity Narrative

As my Area of Excellence, my overall research goals are to understand the processes that distinguish normal and malignant/cancerous cells in order to develop novel therapeutic and preventative agents for the improved treatment of cancer. One of the most exploited differences between normal and cancerous cells is the ability of cancerous cells to grow and divide indefinitely while normal cells have an internal replication clock that eventually stops after a certain number of cellular divisions (termed replicative senescence). The ends of chromosomes, telomeres, have been determined to play a role in this cellular clock in most normal cells. Normal cells exhibit a progressive shortening of telomere lengths, but cancer cells maintain stable telomere lengths. Telomerase is a large RNA/protein complex responsible for maintaining telomeres which is repressed in normal cells yet constitutively active in cancer cells, permitting their immortal phenotype. As discussed in my Candidate's statement, my particular research focus over the past few years has been on therapeutic approaches for breast cancer by targeting telomeres and telomerase as well as reversing the immortal phenotype in cancer by regulating senescence. While in rank, my research efforts have resulted in nearly \$1 million in funding as PI, *a clinical trial on telomerase inhibitors for breast cancer therapy*, as well as 13 refereed publications. Recognition from IUPUI Chancellor Dr. Charles Bantz for my efforts in obtaining extramural funding for my research on telomerase inhibitors as a novel breast cancer therapeutic is included in the Appendix. ***This section includes a more thorough description of my 3-5 significant publications*** of my work on advancing the understanding of the role of telomeres/telomerase in breast cancer research. ***I have also included in this section internal peer evaluation letters*** (as listed below) of my research efforts and accomplishments in breast cancer research, including letters from the co-leaders of the IU Cancer Center Breast Cancer Research Program (Drs. Sledge and Malkas, solicited by the Chair), and the Associate Director of Clinical Trials at IU Cancer Center, Dr. Kathy Miller. *Additional internal peer evaluations* for my research activities include a letter from Dr. Hal Broxmeyer, which is referenced in Section III: Teaching, and a letter from the Associate Director for Basic Science Research for the IU Cancer Center (Dr. Kelley), which is referenced in Section V: Service.

Since my laboratory investigates the processes involved with normal cellular aging and cancer progression, this research encompasses knowledge in senescence, telomeres/telomerase, and generating normal and cancerous cell lines from de-identified patient tissue. To this end, my laboratory has unique skills and resources that have resulted in interdisciplinary research collaborations. ***I have included within this section letters from significant colleagues with whom I collaborate.*** For instance, Drs. George Sledge, Kathy Miller, and Marc Mendonca (Assoc. Professor, IUSM Radiation Oncology) have assisted my research projects on telomerase inhibitors as a novel breast cancer therapeutic or radiation sensitizer for breast cancer. Research chemist Dr. Sergei Gryaznov (Geron Corporation) has provided a letter documenting that he provides reagents as a collaborator for my independent research on telomerase inhibitors and breast cancer. These collaborations have resulted in a clinical trial and significant publications from my laboratory as discussed in this section. As co-investigator on an NIH-R01 grant, I collaborate with Dr. Linda Malkas on understanding DNA replication errors in breast cancer progression, as described in her letter in this section as well as my Candidate Statement.

I have also collaborated with Dr. Robert Bacallao (Assoc. Professor, IUSM Dept of Medicine) on analyzing telomerase activity and developing kidney cell lines from patients with Polycystic Kidney Disease. This work is being prepared for a peer-reviewed publication and these cells have been utilized by other researchers including Dr. Brenda Grimes (Assist. Professor, IUSM Dept of Medical and Molecular Genetics) as described in my Candidate Statement. Based on my expertise on senescence, I have collaborated with Dr. Jalees Rehman (previously a member of the IU Krannert Institute of Cardiology, currently at U. of Chicago) on

the role of oxidative conditions on telomeres and senescence in endothelial cells, which is important for the understanding of stressful diseased conditions within the heart (submitted manuscript). I have also begun collaboration with a fellow member of the IU Center for Regenerative Biology and Medicine, Dr. Randall Roper (Assist. Professor, IUPUI Dept of Biology) on the role of aging and senescence on Down syndrome as modeled in mice. Finally, as my laboratory begins understanding the complex regulation of telomerase in normal and cancer cells via small RNA molecules (microRNAs), I have begun a collaboration with microRNA and cancer expert, Dr. Mircea Ivan (currently at Tufts University) to facilitate my efforts. The interdisciplinary collaborations with Drs. Bacallao, Grimes, Roper, Rehman, and Ivan are expected to *continue over the next 5-10 years, with applications for external federal funding*, as my discoveries on telomerase regulation have potential impact and application in stem cell and tissue regenerative medicine in addition to cancer therapeutics.

2. Peer evaluation of research or creative activities.

In addition to the External peer evaluations letters located in Section I: General Summary (External letters), I have included internal evaluation letters from the following peers:

- Dr. George Sledge (solicited by the Chair)
- Dr. Linda Malkas (solicited by the Chair)
- Dr. Kathy Miller
- Dr. Marc Mendonca
- Dr. Robert Bacallao
- Dr. Mark Kelley (see section V: Service)
- Dr. Hal Broxmeyer (see section III: Teaching)

3. Evidence of scholarly publications and presentations.

Evidence of scholarly publications and presentations are listed in Section I: General Summary (CV; "Invited Lectures" and "Publications") and discussed in Section II: Candidate's statement. First and last author placement on publications, including corresponding/senior authorship, are highly significant in the cancer research field. In addition, significant contributions by a co-investigator/collaborator are identified by the order of the co-authorship. Placement as second author on a manuscript indicates a highly significant contribution by the collaborator (as shown in publications #15, 22, 26, and 27 in the *curriculum vitae*). I have included a more thorough identification and discussion of the three to five most significant publications in rank:

1. **Herbert B-S***, Gellert G, Hochreiter A, Pongracz K, Wright WE, Zielinska D, Chin A, Harley CB, Shay JW, Gryaznov SM. Lipid modification of GRN163, an N3'→P5'-thio-phosphoramidate oligonucleotide, enhances the potency of telomerase inhibition. *Oncogene* 24:5262-5268, 2005 (*corresponding author).

This article was the first to show the efficient inhibition of telomerase in cancer cells without the need for transfection reagents using a modified oligonucleotide targeting the telomerase template. Based on this publication, this lipid-modified oligonucleotide became the lead agent (known as GRN163L) for the Geron-sponsored human clinical trials for the therapy of non-solid and solid tumors. The majority of the work was completed while in rank at IUSM in the Herbert laboratory; the initial experiments began just before I completed postdoctoral studies. I wrote the article and was the corresponding/contributing author on this paper.

2. Hochreiter AE, Xiao H, Goldblatt EM, Gryaznov SM, Miller KD, Badve S, Sledge GW, **Herbert B-S***. The telomerase template antagonist GRN163L disrupts telomere maintenance, tumor growth and metastasis of breast cancer. *Clinical Cancer Research* 12: 3184-3192, 2006 (*corresponding author).

This article was the first to provide a thorough investigation of the lead telomerase inhibitor, GRN163L, in breast cancer cells. The application and translational potential of telomerase inhibitors has garnered much interest in cancer research and it is crucial to understand the effects and mechanisms of this targeted therapeutic as described in this study. In this study, we investigated the effects of GRN163L, a telomerase template antagonist, on a panel of breast cancer cells that are variable in genetic or phenotypic backgrounds, including drug-resistant adenocarcinoma cells. To address the breast cancer translational potential of GRN163L, we employed a breast cancer xenograft and metastasis model that simulates a clinical situation in which a patient arrives with a primary tumor that may be then treated or surgically removed (surgical resection in our mouse model instigates lung metastasis). We found statistical significance of the *in vivo* effects of GRN163L in preventing breast cancer metastases. These results add a significant new body of new and mechanistic data to support the use of GRN163L in solid tumors such as breast cancer. Based on this publication in my laboratory, a clinical trial for GRN163L and breast cancer was proposed, with IUSM being the lead center for the trial. All of the work was performed in my laboratory and I wrote the article as corresponding author.

3. Gomez-Millan J, Goldblatt EM, Gryaznov S, Mendonca MS, **Herbert B-S***. Specific telomere dysfunction induced by GRN163L increases radiation sensitivity in breast cancer cells. *International Journal of Radiation Oncology, Biology, Physics* 67: 897-905, 2007 (*corresponding author).

As the telomerase template antagonist GRN163L enters human cancer clinical trials as the first rationally designed telomerase inhibitor, it is important to test whether GRN163L can be effective in combination with other conventional therapies. In this study, we tested whether telomerase inhibition and telomere dysfunction by GRN163L could sensitize breast cancer cells to irradiation, from a radiobiological point of view. We analyzed cells treated with the telomerase template antagonist GRN163L for different periods of time. We showed with clonogenic assays that telomere dysfunction induced by GRN163L enhances the effect on ionizing radiation (IR). Our findings also suggest that short-term treatment with GRN163L does not enhance the effects of IR per se, but significantly decreases the proliferation rate. This was the first report demonstrating synergistic and additive effects of telomerase inhibition by GRN163L and irradiation. These results offer new clinical implications for GRN163L and possible applications to different clinical settings. All of the work was performed directly under Dr. Herbert's supervision, with Dr. Gomez-Millan performing the radiation biology/survival analyses with Dr. Herbert/Erin Goldblatt, Erin Goldblatt performed the *in vivo* experiments and all telomerase inhibitor experiments, and Dr. Herbert wrote and was the corresponding author. This study provided the rationale for the design and feasibility for clinical trials on GRN163L in combination with other therapeutic agents.

4. **Herbert B-S***, Hochreiter AE, Wright WE, Shay JW. Non-radioactive detection of telomerase activity using the Telomeric Repeat Amplification Protocol (TRAP). *Nature Protocols* 1: 1583-1590, 2006 (*corresponding author).

This article described a real-time method to measure telomerase activity without the use of radionucleotides, making this TRAP assay readily translatable for large volume samples and clinical diagnostic/prognostic use. The original, radioisotope version of the TRAP telomerase activity assay was patented by Drs. Wright and Shay. This article has already been cited multiple

times and reprints have been requested by leaders in the telomerase in aging and cancer field (e.g., Dr. David Beach, London Queen Mary's School of Medicine and Dentistry; Dr. Dorothy Shippen, Texas A&M). I have assisted multiple academic research laboratories on this assay and have been acknowledged in papers published in *Molecular Cell Biology*, for example. All of the work was performed in my laboratory and I wrote the article as corresponding/contributing author.

5. **Herbert B-S***, Goldblatt EM. Therapeutic targets and drugs- Telomerase: Telomerase inhibitors including telomerase associated protein inhibitors. In *Cancer Drug Discovery and Development: Telomeres and Telomerase in Cancer*. Humana Press, Springer Science and Business Media, New York, NY, in press 2008 (*corresponding author).

As an expert in the field, I was invited to contribute a book chapter on the subject of telomerase inhibitors for the audience of oncologists and clinical researchers. This book chapter is the most current and comprehensive writing on the history and use of telomerase inhibitors as cancer therapeutics. The book is published under Springer Science/Humana Press which is the largest academic book publisher in the world.

4. Evaluation of stature of journals in which publications appear or galleries in which showings have been presented.

The stature of journals in which publications appear is included at the end of this section. Publications that I have authored have been cited for 941 times, with an average 31.37 per item according to the Web of Science database of the Institute for Scientific Information (ISI). For citations during 2003-2008 (while in rank), publications that I have authored have been cited 174 times. The citation report as of April 2008 is included in the Appendix.

5. Research load information; amount of time devoted to research.

At least 90% of my time is devoted to research activities. This effort includes direct conduct of research in the laboratory, performing experiments, and supervising students and fellows in the laboratory on projects that are a part of my research program. In addition, my research load includes analyzing data, submitting *quarterly and yearly reports* for the NIH-N01 funded proposal, writing grant proposals (see Appendix for list of grants submitted while in rank), and writing scientific manuscripts (see internal letters in this section and CV for evidence of productivity). I am also a co-investigator on other research projects within the department, IUSM, cancer center, and as a new member of the IU Center for Regenerative Biology and Medicine.

6. Documentation of individual contributions to collaborative work.

As stated in Section II: Candidate's statement and this section, my research has impacted the work of other colleagues around campus as well as other institutes. I have included letters from these colleagues as documentation of my individual contributions of our collaborations:

- Dr. George Sledge
- Dr. Linda Malkas
- Dr. Kathy Miller
- Dr. Marc Mendonca
- Dr. Robert Bacallao
- Dr. Brenda Grimes (see Appendix)
- Dr. Randall Roper
- Dr. Sergei Gryaznov
- Dr. Jalees Rehman
- Dr. Mircea Ivan (see Appendix)

EVALUATION OF STATURE OF JOURNALS IN WHICH PUBLICATIONS APPEAR

The journals in which Dr. Herbert has published full papers while in rank at IUSM had the following Impact Factors for 2006, according to the Institute for Scientific Information (ISI):

Journal Name	Impact Factor
<i>Aging Cell</i>	6.276
<i>Breast Cancer Research and Treatment</i>	4.671
<i>Cancer Research</i> (10 th of 126 in oncology journals)	7.656
<i>Clinical Cancer Research</i> (13 th of 126 in oncology journals)	6.177
<i>International Journal of Biochemistry and Cell Biology</i>	4.804
<i>International Journal of Radiation Oncology, Biology, Physics</i>	4.463
<i>Mechanisms of Aging and Development</i>	3.846
<i>Nature Protocols</i>	too new for ranking
<i>Nucleosides, Nucleotides & Nucleic Acids</i>	0.671
<i>Oncogene</i> (12 th of 127 in oncology journals)	6.582
<i>Proceeding of the National Academy of Sciences USA</i>	9.643
<i>Urologic Oncology</i>	2.089

Most of the journals in which Dr. Herbert publishes are the top scientific journals for the field of cancer research.

Journal descriptions:

Aging Cell

Published on behalf of the Anatomical Society of Great Britain and Ireland, *Aging Cell* publishes novel and exciting science which addresses fundamental issues in the biology of aging. The ISI Journal Citation Reports® Ranking in 2006: 32/156 (Cell Biology); 2/30 (Geriatrics & Gerontology). The Impact Factor is 6.276. It is one of the highest rated specialty journals for the aging research field.

Breast Cancer Research and Treatment

Breast Cancer Research and Treatment, by Springer publishing group, is the premier international journal that focuses on the unique problems of breast cancer, covering all of the various disciplines of breast cancer. Editor-in-Chief: Marc E. Lippman (University of Miami, Miller School of Medicine, Miami, FL, USA). Associate Editors: Stephen P. Ethier (Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA); Daniel F. Hayes (University of Michigan Health System, Ann Arbor, MI, USA). The Impact factor of this journal is 4.671. It ranks 28th of 126 in oncology journals (ISI Journal Citation Reports® Ranking in 2006). It is one of the highest-rated specialty journals for the breast cancer research field.

Cancer Research

Cancer Research, an official journal of the American Association for Cancer Research (the premier cancer research society), is the most frequently cited cancer journal in the world. The journal publishes significant, original studies on all areas of basic, clinical, translational, epidemiological, and prevention research in cancer and the cancer-related biomedical sciences.

Papers are stringently reviewed, and only those that report results of novel, timely, and significant research and meet high standards of scientific merit are accepted for publication. It ranks 10th of 126 in oncology journals (ISI Journal Citation Reports® Ranking in 2006). The Impact factor of this journal is 7.656. It is the top-ranked, premier journal in the field of cancer research.

Clinical Cancer Research

Clinical Cancer Research, an official journal of the American Association for Cancer Research (the premier cancer research society), publishes original articles describing clinical research on the cellular and molecular characterization, prevention, diagnosis, and therapy of human cancer. Its focus is on innovative clinical research and translational research that bridges the laboratory and the clinic. It publishes on clinical trials evaluating new treatments for cancer; research on molecular abnormalities that predict incidence, response to therapy, and outcome; and laboratory studies of new drugs and biological agents that will lead to clinical trials in patients. It ranks 13th of 126 in oncology journals (ISI Journal Citation Reports® Ranking in 2006). The Impact factor of this journal is 6.177. It is an excellent, top-ranked cancer research society journal.

International Journal of Biochemistry and Cell Biology

The International Journal of Biochemistry & Cell Biology (formerly known as *International Journal of Biochemistry*) commenced publication 1970 and publishes papers containing the results of original research in all areas of contemporary biochemistry and cell biology. The scope includes biochemical, cellular and molecular approaches to the study of cells and subcellular processes, and all areas of biomedical research. The Impact factor of this journal is 4.804 (Journal Citation Reports® 2007, published by Thomson Scientific). The ISI Journal Citation Reports® Ranking for 2006: 39/156 (Cell Biology); 56/262 (Biochemistry & Molecular Biology). It is a premier journal for pure and applied scientists with a research interest in any aspect of modern biochemistry and cell biology.

International Journal of Radiation Oncology, Biology, Physics

The Official Journal of the American Society for Therapeutic Radiology and Oncology. *International Journal of Radiation Oncology*Biological*Physics (IJROBP)*, known in the field as the “Red Journal,” offers authoritative articles linking new research and technologies to clinical applications. Original contributions by leading scientists and researchers include, but are not limited to, experimental studies of combined modality treatment, tumor sensitization and normal tissue protection, molecular radiation biology, tumor biology, and clinical investigations. The journal has an impact factor of 4.463 is ranked in the top 10th percentile for Radiology, Nuclear Medicine and Medical Imaging titles, and in the top 25th percentile for Oncology titles, according to the 2006 Journal Citation Reports®, published by Thomson Scientific. It is an excellent premier journal for the cancer biology and radiation oncology field.

Mechanisms of Aging and Development

Mechanisms of Ageing and Development, by Elsevier Publishing Group, is a multidisciplinary journal aimed at revealing the molecular, biochemical, and biological mechanisms that underlie the process of ageing and the development of age-associated disease. Emphasis is placed on investigations that delineate the contribution of (1) oxidative damage and/or cellular metabolism; (2) genetic instability; (3) telomere integrity; (4) mitochondrial function; (5) genetic programs.

The Editor in chief is Vilhem A. Bohr, Laboratory of Molecular Gerontology National Institute on Aging. The 2006 Impact factor of this journal is 3.846. The ISI Journal Citation Reports® Ranking for 2006: 50/156 (Cell Biology); 5/30 (Geriatrics & Gerontology). It is an excellent, top-ranked specialty journal for the aging research field.

Nature Protocols

Nature Protocols, a part of the Nature Publishing Group, aims to publish the protocols being used to answer outstanding biological and biomedical science research questions, including methods grounded in physics and chemistry that have a practical application to the study of biological problems. The core content is high quality, peer-reviewed procedures. Nature Protocols initiated in 2006 and it was too new for the 2007 Thomson Journal Citation Reports. It is indexed through PubMed/Medline and part of *Nature* Journals family.

Nucleosides Nucleotides and Nucleic Acids

Nucleosides, Nucleotides & Nucleic Acids, by the Taylor and Francis publishing group, is the official publication for the International Society Nucleosides, Nucleotides and Nucleic Acids. It publishes monthly research articles that focus on the chemistry and biology of nucleosides, nucleotides, nucleic acids, and significant observations related to new compounds. The impact factor is 0.671.

Oncogene

Oncogene, a part of the Nature Publishing Group, publishes the latest developments in cancer research. It covers all aspects of the structure and function of oncogenes/oncology, especially: cellular oncogenes and their mechanism of activation; structure and function of their encoded proteins; oncogenes of the DNA and RNA tumour viruses; the molecular oncology of human tumours; tumour suppressor genes; growth regulatory genes; cell cycle control; growth factors and receptors; apoptosis; immortalization and cellular senescence. The 2006 Impact Factor is 6.582 (Journal Citation Reports, Thomson 2007) and ranks 12/127 in Oncology, 17/131 in Genetics & Heredity, 29/156 in Cell Biology, and 34/262 in Biochemistry & Molecular Biology journals. It is one of the top-ranked, primary tier journals in the cancer research field.

Proceeding of the National Academy of Sciences USA (PNAS)

PNAS is one of the world's most-cited multidisciplinary scientific serials. Since its establishment in 1914, it continues to publish cutting-edge research reports, commentaries, reviews, perspectives, colloquium papers, and actions of the Academy. Coverage in PNAS spans the biological, physical, and social sciences. PNAS is published weekly in print, and daily online in PNAS Early Edition. The PNAS impact factor is 9.64 for 2006. It ranks 3rd out of 49 in Multidisciplinary Sciences journals (after *Science* and *Nature*; ISI Journal Citation Reports® Ranking in 2006). It is a top-tier scientific research journal.

Urologic Oncology

Urologic Oncology: Seminars and Original Investigations is the official journal of the Society of Urologic Oncology. The publication delivers timely original clinical research articles and up-to-date comprehensive reviews of critical scientific relevance. All articles are of significant interest to all clinicians involved in the practice of urologic oncology including urologists, oncologist and radiologists. The impact factor is 2.089 for 2006; it is a secondary journal for the oncology field.

CURRICULUM VITAE

NAME: Herbert, Brittney-Shea

EDUCATION:

UNDERGRADUATE: The University of Texas at Austin
B.A. Biology
1993

GRADUATE: The University of Texas at Austin
Ph.D. Biological Sciences
1998

POSTDOCTORAL: The University of Texas Southwestern Medical Center at Dallas
Cell Biology
1998-2003

ACADEMIC APPOINTMENTS:

09/2002-08/2003: Instructor (non-tenure track), Department of Cell Biology
The University of Texas Southwestern Medical Center at Dallas

09/2003-present: Assistant Professor, Department of Medical and Molecular Genetics
Indiana University School of Medicine, Indianapolis, IN

2003-present: Member, University Graduate School Faculty, Indiana University

HOSPITAL APPOINTMENTS: not applicable

OTHER APPOINTMENTS AND PROFESSIONAL CONSULTANSHIPS:

2003-2006: Associate Member, Indiana University Cancer Center, Indianapolis, IN

2007-present: Full Member, Indiana University Melvin and Bren Simon Cancer
Center (IUSCC), Indianapolis, IN

2008-present: Member, Indiana University Center for Regenerative Biology and
Medicine, Indianapolis, IN

SPECIALTY BOARD STATUS: not applicable

LICENSURE AND CERTIFICATION: not applicable

PROFESSIONAL ORGANIZATIONS:

Sigma Xi, The Scientific Research Society
American Association for Cancer Research (AACR)
AACR Women in Cancer Research
American Society of Human Genetics

HONORS AND AWARDS:

1994-1997	NASA Graduate Student Researchers Program Fellow
1997-1998	The University of Texas at Austin University Continuing Fellow
1997	The UT Zoology Scholarship for Excellence in Research Award
1997-present	The University of Texas at Austin Friar Society (oldest honor society at UT)
1998	American Society for Clinical Nutrition Young Investigator Finalist Award
1998	UT Office of Graduate Studies Professional Development Award
1999-2000	Susan G. Komen Breast Cancer Foundation Postdoctoral Fellow
2000-2003	U.S. Dept of Defense Breast Cancer Research Program Postdoctoral Fellow
2001-present	Who's Who in America, American Women, Medicine and Healthcare, Science and Engineering,
2002	American Assoc. for Cancer Research-AFLAC Scholar-in-Training Award
2003	American Assoc. for Cancer Res Pathobiology of Cancer Workshop Fellow
2004-2005	Leadership in Academic Medicine Program (LAMP) at IUSM Fellow

TEACHING ASSIGNMENTS:

1) Coursework

Fall 2003	Q640: Special Topics in Human Genetics 3 credits, one semester course Enrollment: 2 Ph.D. graduate students Prepared and taught one lecture (1 contact hour): "Understanding the Role of telomeres in human aging and cancer."
Spring 2004	Q620: Human Cytogenetics 3 credits, one semester course Enrollment: 18 graduate students (17 Genetics M.S. and Ph.D. students and 1 Biochemistry Ph.D. student) Prepared and taught one lecture (1 contact hour): "The Telomere."
Fall 2004	Q640: Special Topics in Human Genetics 3 credits, one semester course Enrollment: 5 Ph.D. graduate students Prepared and taught one lecture (1 contact hour): "Understanding the role of telomerase in breast cancer."
Fall 2004	Q622: Cytogenetics of Malignancies 3 credits, one semester course Enrollment: 9 Ph.D. graduate students (1 Physiology, 1 Anatomy, 7 Biochemistry) Prepared and taught one lecture (1.5 contact hours): "Telomerase and Cancer."
Fall 2005	Q640: Special Topics in Human Genetics 3 credits, one semester course Enrollment: 5 Ph.D. genetic graduate students Prepared and taught one lecture (1 contact hour): "Understanding the role of telomerase in breast cancer."

- Spring 2006 Q620: Human Cytogenetics
3 credits, one semester course
Enrollment: 26 graduate students (25 Genetics M.S. and Ph.D. students and 1 Microbiology Ph.D. student)
Prepared and taught one lecture (1.5 contact hours): “The Telomere”
- Spring 2006 Q640: Special Topics in Human Genetics (Concepts in Genetics)
3 credits, one semester course
Enrollment: 5 M.S./Ph.D. genetic graduate students
Prepared and taught one lecture (1.5 contact hours): “Tumor Suppressor Genes and Oncogenes”
- Fall 2006 Q622: Cytogenetics of Malignancies
3 credits, one semester course
Enrollment: 10 graduate students (Biochemistry, Microbiology Ph.D. students)
Prepared and taught one lecture (1 contact hours): “Telomerase and Cancer”
- Fall 2006 Q640: Special Topics in Human Genetics (“Molecular Cancer Genetics”;
course director)
1 credit, one module (one third of semester)
Course cancelled due to limited enrollment
Designed course curriculum of 10 lectures-used for G724
- Fall 2006 Q640: Special Topics in Human Genetics
3 credits, one semester course
Enrollment: 3 M.S./Ph.D. graduate students
Prepared and taught one lecture (1 contact hour): “Cellular Senescence as a Tumor Suppressor Mechanism”
- Spring 2008 G724: Molecular Cancer Genetics (Co-Course director)
1 credit, one module (one third of semester)
Enrollment: 14 graduate students (2 MS, 1 MD/PhD, and 11 PhD)
Designed course curriculum, handled logistics (paperwork, room, etc), monitored all lectures; prepared and taught 4 lectures; prepared, proctored and graded exam (20 contact hours)
- Spring 2008 Q620: Human Cytogenetics
3 credits, one semester course
Enrollment: 18 students (MS Genetic Counseling, MS, PhD, and fellows)
Prepared and taught one lecture (1.5 contact hours): “The Telomere”
- Spring 2008 G852: Concepts of Cancer Biology: Signaling Gone Awry
2 credits, two modules (two-thirds of semester)
Enrollment: 22 PhD graduate students

Prepared and taught one lecture (2 contact hours): “Immortalization: Telomerase: How to make a cancer cell in vitro”; prepared and graded 1 exam question

Spring 2008 Cytogenetics Laboratory elective
Enrollment: 6 Pathology M.D. residents
Prepared and taught one lecture (1.5 contact hours): “Use of Telomerase and Telomeres in Diagnostics and as Targets for Therapy”

2) Research Supervised in courses Q800 (Medical and Molecular Genetics Research) or G594 (Research in Medical Science for M.S. in Medical Sciences):

Spring 2004 Q800: Maria Britain (1 credit)
Fall 2004 Q800: Erin Goldblatt (1 credit)
Spring 2005 Q800: Erin Goldblatt (1 credit)
Spring 2005 Q800: Christian Carbe (1 credit)
Fall 2005 Q800: Anuradha Ramamoorthy (1 credit)
Summer 2007 Q800: Carla Mangum (4 credits)
Spring 2008 G594: Christina B. Smith (3 credits)
Summer 2008 Q800: Carla Mangum (4 credits)

PROFESSIONAL SERVICE:

1) Service to the discipline (national/international)

a) Grant Peer Review Study Sections:

2004-present California Breast Cancer Research Program (CBCRP) Grant Peer Review Committee (Tumor Progression, Pathogenesis committees)
2007 Mary Kay Ash Foundation Grant Peer Review Committee
2007 Israel Science Foundation *ad hoc* grant reviewer (expert for a telomere/telomerase grant)
2007 U.S. Dept of Defense Congressionally Directed Medical Research Programs scientific peer review for the 2007 Breast Cancer Research Program: Molecular Biology and Genetics Grant Review Panel (MBG-4)
2008 Association for International Cancer Research (UK) *ad hoc* grant reviewer (expert for a telomerase/dyskerin and cancer grant)

b) Scientific Meetings leadership:

2004 Chairperson, Session II: Telomerase Diagnostics and Therapeutics, American Association for Cancer Research (AACR) Special Conference “The Role of Telomeres and Telomerase in Cancer,” San Francisco, CA (Nov 3-7, 2004)
2006 Co-organizer: 8th Annual Midwest DNA Repair Symposium (AMDRS); Indianapolis, IN (May 20-21, 2006)
2006 Discussion Panel: British Association for Cancer Research Conference: “Telomerase and Cancer Stem Cells,” York, UK (September 4, 2006)

c) Ad hoc Scientific Manuscript Reviewer (while in rank) for:

1. *BioDrugs Journal*
2. *BMC Cell Biology*
3. *Cancer Research* (American Association for Cancer Research journal)
4. *Clinical Cancer Research* (American Association for Cancer Research journal)
5. *Critical Reviews in Oncology/Hematology*
6. *DNA and Cell Biology*
7. *European Surgical Research*
8. *Experimental Hematology*
9. *Journal of Molecular Diagnostics*
10. *Life Sciences*
11. *Methods in Molecular Biology* (2 book chapters)
12. *Molecular and Cellular Biology*
13. *Molecular Cancer Research* (American Association for Cancer Research journal)
14. *Molecular Cancer Therapeutics* (American Association for Cancer Research journal)
15. *Molecular Pharmacology*
16. *Neoplasia*
17. *Oncogene*

2) Service to patients/clients and related clinical institutions

None

3) Service to the community

- | | |
|-----------------|--|
| September, 2004 | Host for Laura Mass, Pike High School (Indianapolis) senior who shadowed me for the day |
| May, 2005 | Exhibit volunteer/presenter for “Genome: The Secret of How Life Works” at the Indiana State Museum, Indianapolis, IN |
| March, 2006 | Host for Emily Henry, Westfield High School (Indianapolis) senior who shadowed me for the day |
| 2007-present | Community outreach at the Indiana State Fair, IU at the Indiana State House Day, and Mini-Medical School through the Faculty Community Relations Committee |

UNIVERSITY SERVICE:

1) Departmental:

- | | |
|--------------|---|
| 2003-present | Department of Medical and Molecular Genetics M.S./Ph.D. Graduate Student Admissions Committee, member |
| 2003-present | Dept of Medical and Molecular Genetics Preliminary Examination grader |
| 2004-present | Host for Dept Seminar speakers (hosted four speakers over four years) |
| 2006, 2008 | Research Associate search and screen committee |
| 2008 | Kinsley Ph.D. Thesis Award nominating committee |
| 2008-present | Dept of Medical and Molecular Genetics Seminar Series co-coordinator |

2) School of Medicine:

- | | |
|-----------|---|
| 2003-2005 | IU School of Medicine (IUSM) Security/Contingency Planning Committee |
| 2004 | IUSM Dept of Biochemistry and Molecular Biology Research Day-poster judge |

2006 IUSM Chapter Sigma Xi Research Competition Judge (student presentations)
 2007-present IUSM Faculty Community Relations Committee, elected by the faculty
 2007-present IUSM Faculty Steering Committee, member
 2007-present IUSM/Indiana Biomedical Gateway (IBMG) Ph.D. graduate student applicant interviewer

3) Institutional/IUPUI Campus:

2006-present Institutional Biosafety Committee (IBC), full member
 2006 IU Simon Cancer Center (IUSCC)-Purdue University Cancer Center Pilot Study Proposals Grant reviewer
 2006-present IUSCC Breast Cancer Research Program Speaker Coordinator
 2007 IUSCC V Foundation nomination committee
 2008 IUSCC Cancer Research Day poster judge

4) Student Service:

a) Graduate Student Advisory/Research/Dissertation Committees:

<u>Dates</u>	<u>Student's Name</u>	<u>Department</u>	<u>Role</u>
2003-2007	Guiandre Joseph	M.D./Ph.D. in Microbiology & Immunology, defended thesis June 2007	Member
2004-present	Erin Goldblatt	Ph.D. in Department of Medical and Molecular Genetics	Chair
2005-2006; 2008-present	Anuradha Ramamoorthy	Ph.D. in Department of Medical and Molecular Genetics	Advisory Chair; Member
2005-present	Holly Martin	Ph.D. in Department of Medical and Molecular Genetics	Member
2005-present	Tabitha Hardy	Ph.D. in Microbiology & Immunology	Member
2005-present	Catherine Steding	Ph.D. in Microbiology & Immunology	Member
2008-present	Bill Ranahan	Ph.D. in Biochemistry and Molecular Biology	Member
2007-present	Carla Mangum	M.S. Jackson State University (NIH R25 Bridges to Doctorate Program with IUSM)	Member

b) Predoctoral Students Supervised (research):

2005-present Erin Goldblatt, Medical and Molecular Genetics (Ph.D.)
 2007-present Carla Magnum, IUSM/Jackson State Bridges to Doctorate Program (M.S.)
 2008 Christina B. Smith, G594 course mentor, IU Medical Sciences Program (M.S.)

c) Postdoctoral Researchers Supervised:

2007-2008 Saleha Vuyyuri, Ph.D.

d) Undergraduate/Summer Student Research Supervised:

2004-2005 Alacia Whitehair, IUPUI Biology; currently an M.D. student in Florida
2004 Danielle Harvey, IUSCC Summer Research Program; currently a Texas Southern University Biology Pre- Medicine Major
2005 Tory Caudle, IU Summer Biomedical Research Program; currently an M.D. student at IUSM
2006 Priscilla Erickson, Kenyon College, Ohio; currently an undergraduate at Kenyon College
2007 Oluwaranti "Ranti" Ositelu, IUSCC Summer Research Program; currently a high school student at The Culver Academies, Westfield, IN

OTHER PROFESSIONAL ACTIVITIES:

1) Invited Seminars:

2003

1. Indiana University Cancer Center, "Telomerase: A Breast Cancer Therapeutic and Chemopreventive Target" (September 24, 2003)
2. **American Society of Cell Biology (ASCB)** Annual Meeting in San Francisco, "Telomeres and how to pass crisis" (December 13, 2003)-Mini Symposia lecture

2004

3. Indiana University School of Medicine Department of Biochemistry & Molecular Biology, "Telomerase: A Breast Cancer Therapeutic and Chemopreventive Target" (April 12, 2004)

2006

4. Indiana University School of Medicine Division of Cytogenetics In-service Educational Unit, "Telomerase and the Immortal Phenotype of Breast Cancer: Insights from Genetic Susceptibility Models" (January 12, 2006)
5. Indiana University Cancer Center Tumor Microenvironment Program, "Maintenance of the Immortal Phenotype in Breast Cancer: a Telocentric Point of View" (February 22, 2006)
6. Indiana University at Bloomington Medical Sciences, "Maintenance of the Immortal Phenotype in Breast Cancer: a Telocentric Point of View" (February 27, 2006)
7. Geron Corporation (Menlo Park, CA), "Consequences of GRN163L Treatment in Breast Cancer" (April 25, 2006)
8. **British Association for Cancer Research** (York, UK) Conference on Telomerase and Cancer Stem Cells: Exploiting Cellular Immortality for Therapeutic Gain, "How do we measure Telomeres and Telomerase?" (September 5, 2006)

9. IUPUI Dept of Biology (Indianapolis, IN), “Telomerase and the Immortal Phenotype of Breast Cancer: Models and Novel Therapies” (November 17, 2006)

10. IUSM Dept of Microbiology (Indianapolis, IN), “Telomerase and Breast Cancer: Impact on Immortalization, Targets, and Microenvironment” (December 7, 2006)

2007

11. **Virginia Commonwealth University Pathology Grand Rounds** (Richmond, VA), “Mechanisms of Action of Telomerase Template Antagonists in Breast Cancer: Insights into Rational Combination with Chemotherapy” (November 30, 2007)

2008

12. IUPUI Dept of Biology (Indianapolis, IN), “How to Bypass Senescence: the Role of Telomeres and Telomerase in Cellular Aging” (March 22, 2008)

13. **Hematology/Oncology Grand Rounds, Henry Ford Health System** (Detroit, MI), “Exploiting Telomerase for Cancer Therapeutics and Prognosis” (May 30, 2008)

14. **British Association for Cancer Research** Conference on Cellular Immortality & Cancer: From Telomerase to Cancer Stem Cells (Stratford upon Avon, UK), “Targeting Telomerase and Senescence Mechanisms in Breast Tumor-Initiating Cells” (June 4, 2008)

2009

15. **Second International Meeting on Quadruplex DNA** (Louisville, KY), April 18-21, 2009)-Major Symposia lecture

2) Media Interviews:

2007 Featured in the *Indianapolis Star* on my research mapping and success with the IU Simon Cancer Center’s ITRAC (IU Translational Research Acceleration Collaboration)

2008 Interviewed by the Vera Bradley Breast Cancer Foundation, which helps supports the Breast Cancer Program at IUSCC, on my research in breast cancer at IUSCC for their magazine publication (vol 3, 2008), national fundraising event and website

2008 Featured in the inaugural newsletter for the IU Center for Regenerative Biology and Medicine on my research on cellular immortalization and telomerase

GRANTS AND FELLOWSHIPS:

ACTIVE:

1. 05/01/2008-03/01/2010

Geron Corporation Investigator-Initiated Sponsored Research Project

Title: A Study of Telomerase Inhibition in Circulating Tumor Cells after Treatment with GRN163L in the Geron-sponsored CP14A010 Study

Amount: \$18,727 direct (yr1); \$25,000 total (yr1)
Principal Investigator: Brittney-Shea Herbert (<1% effort)

2. 05/01/2008-10/31/2009
OC073179
U.S. Department of Defense Congressionally Directed Medical Research Programs
Title: Inhibition of Ovarian Cancer by MircoRNA-Mediated Regulation of Telomerase
Amount: \$75,000 direct (yr1); \$113,625 total (yr1)
Principal Investigator: Brittney-Shea Herbert (20% effort)
3. 11/01/2006-10/31/2008
NO1 CN43300-N2007-16
NIH-National Cancer Institute
Title: Mechanism-based *in vitro* screening of chemopreventive agents for the inhibition/reversal of the tumorigenic phenotype in ER α -negative human mammary epithelial cells; Project N2007-16
Amount: \$335,870 total direct; \$448,386 total
Principal Investigator: Brittney-Shea Herbert (40% effort)
4. 07/01/2006-06/30/2008; 1 yr no-cost extension
Mary Kay Ash Charitable Foundation
Title: Targeting Telomerase in Breast Cancer Stem Cells: Inhibition of Breast Tumor Recurrence and Metastasis
Amount: \$86,956 total direct; \$100,000 total
Principal Investigator: Brittney-Shea Herbert (10% effort)
5. 01/05/2007-03/01/2010
Geron Corporation Investigator-Initiated Sponsored Research Project
Title: Dysfunctional Telomeres and the Anti-Cancer Effects of Telomerase Inhibitors
Amount: \$93,576 direct (yr1); \$124,924 total (yr1)
Principal Investigator: Brittney-Shea Herbert (10% effort)
6. 08/01/2007-07/31/2012
NIH 1R01CA121289
NIH-National Cancer Institute
Title: A Structure/Function Analysis of a Tumor Specific Protein
Amount: \$950,000 total direct; \$1,439,250 total
Principal Investigator: Linda Malkas
Role: co-Investigator (5% effort)
7. 07/01/1999-06/30/2009
NIH 5T32HL007910
NIH-National Heart, Lung, and Blood Institute
Title: Basic Science Studies on Gene Therapy of Blood Diseases
Principal Investigator: Hal Broxmeyer
Role: Preceptor (1% effort)

8. 06/01/2003-07/31/2009
NIH 5R25GM067592
NIH-National Institute of General Medical Sciences
Title: Bridges to Doctorate at IU School of Medicine
Principal Investigator: Hal Broxmeyer
Role: Preceptor (3% effort)

COMPLETED:

1. 05/15/2007-06/14/2007
csKeys, Inc. (external)
Title: caPCNAab versus Peptide and Small Molecule Immunofluorescence Validation Study
Amount: \$3,300 total direct; \$5,000 total
Principal Investigator: Brittney-Shea Herbert (1% effort)
2. 07/01/2006-06/30/2007
IUSM Translational Research Fellowship
Title: Telomere Independent Effects of Telomerase Antagonist Treatment: Implications for Augmenting Chemosensitivity in Breast Cancer
Amount: \$22,500 stipend
Principal Investigator: Erin Goldblatt (Ph.D student)
Role: Mentor
3. 07/01/2005-06/30/2007
Showalter Research Trust Fund
Title: Targeting telomerase for breast cancer treatment
Amount: \$50,000 total direct; \$60,000 total
Principal Investigator: Brittney-Shea Herbert (10% effort)
4. 07/01/2004-08/31/2005
Phi Beta Psi National Society for cancer research (external)
Title: Combining telomerase inhibitors and chemotherapies as effective breast cancer treatments
Amount: \$47,000
Principal Investigator: Brittney-Shea Herbert (5% effort)
5. 07/01/2004-12/31/2005
IRG-84-002-19
American Cancer Society
Title: Telomerase inhibition and induced senescence/apoptosis in breast cancer
Amount: \$23,285
Principal Investigator: Brittney-Shea Herbert (10% effort)
6. 07/01/2004-06/30/2006
Biomedical Research Pilot Fund, Indiana University School of Medicine

Title: Gene expression profiles in a human mammary epithelial cell cancer progression series
Amount: \$10,000
Principal Investigator: Brittney-Shea Herbert (10% effort)

7. 07/15/2005-07/14/2006

Biomedical Research Grant, Indiana University School of Medicine
Title: Dysfunctional telomeres as a novel target in cancer therapeutics
Amount: \$40,000
Principal Investigator: Brittney-Shea Herbert (10% effort)

8. 07/01/2000-06/30/2003

DAMD17-00-1-0438
U.S. Department of Defense Congressionally Directed Medical Research Programs
Title: Do Telomerase Inhibitors Prevent the Spontaneous Immortalization of Breast Epithelial Cells from Individuals Predisposed to Breast Cancer?
Principal Investigator: Brittney-Shea Herbert

9. 09/01/1999-06/30/2000

PDF99-003061
Susan G. Komen Breast Cancer Foundation (*declined yrs 2-3 in lieu of DOD award*)
Title: Do Tamoxifen and Telomerase Inhibitors Prevent the Spontaneous Immortalization of Breast Epithelial Cells Obtained from Individuals Predisposed to Breast Cancer?
Principal Investigator: Brittney-Shea Herbert

10. 07/01/1994-06/30/1997

NASA NGT 51365
NASA Graduate Student's Researchers Program
Title: RRR- α -tocopheryl succinate modulation of TGF- β and the TGF- β receptors in Human Myelocytic Leukemia (HL-60) Cells
Principal Investigator: Brittney-Shea Herbert

PENDING SUPPORT:

1. 10/01/2008-09/30/2010

AACR-The Breast Cancer Research Foundation
Combined Telomerase and VEGF Inhibition in Metastatic Breast Cancers
Amount: \$226,879 total direct; \$250,000 total
Principal Investigator: Brittney-Shea Herbert (15% effort)

2. 10/01/2008-09/30/2010

The Breast Cancer Research Foundation
A Study of Telomerase Inhibition in Circulating tumor Cells After Treatment with GRN163L
Amount: \$208,333 total direct; \$250,000 total
Principal Investigator: Kathy Miller
Role: co-Investigator (10% effort)

3. 04/01/2009-03/31/2011
PCRPA Idea Award
U.S. Department of Defense Congressionally Directed Medical Research Programs
Epigenetic Regulation in Prostate Cancer Development and Metastasis
Amount: \$375,000 total direct; \$566,250 total
Principal Investigator: Meei-Huey Jeng
Role: co-Investigator (5% effort)
4. 04/01/2009-03/31/2011
BCRP Idea award
U.S. Department of Defense Congressionally Directed Medical Research Programs
Regulation of Telomerase in Breast Cancer by CARM1
Amount: \$375,000 total direct; \$566,250 total
Principal Investigator: Meei-Huey Jeng
Role: co-Investigator (5% effort)
5. 04/01/2009-03/31/2011
BCRP Idea Award
U.S. Department of Defense Congressionally Directed Medical Research Programs
A Novel Biomarker for the Early Detection of Breast Cancer
Amount: \$375,000 total direct; \$566,250 total
Principal Investigator: Robert Hickey
Role: co-Investigator (10% effort)
6. 05/01/2009-04/30/2011
NO1 CN43300-N2007-16
NIH-National Cancer Institute
Title: Mechanism-based *in vitro* screening of chemopreventive agents for the inhibition/reversal of the tumorigenic phenotype in ER α -negative human mammary epithelial cells; Project N2007-16
Amount: \$335,870 total direct; \$448,386 total
Principal Investigator: Brittney-Shea Herbert (30% effort)

PRINT AND ELECTRONIC PUBLICATIONS (cited ~941 times, Ave 31.37 per item):

I. TEACHING: none

II. RESEARCH, SCHOLARSHIP, OR CREATIVE ACTIVITIES (Refereed Journals)

1. **Herbert B-S**, Sanders BG, Kline K. N-(4-Hydroxyphenyl)retinamide (4-HPR) activation of transforming growth factor- β (TGF- β) and induction of apoptosis in human breast cancer cells. *Nutrition and Cancer* 34: 121-132, 1999.
2. **Herbert B-S**, Pitts AE, Baker SI, Hamilton SE, Wright WE, Shay JW, Corey DR. Inhibition of human telomerase in immortal human cells leads to progressive telomere shortening and cell death. *Proc Natl Acad Sci* 96:14276-14281, 1999.

3. Ouellette M, Liao M, **Herbert B-S**, Johnson M, Holt SE, Liss HS, Shay JW, Wright WE. Subsenescent telomere lengths in fibroblasts immortalized by limiting amounts of telomerase. *J Biol Chem* 275:10072-10076, 2000.
4. **Herbert B-S**, Wright AC, Passons CM, Kopelovich L, Ali I, Wright WE, Shay JW. Effects of chemopreventive and anti-telomerase agents on the spontaneous immortalization of breast epithelial cells. *J Natl Cancer Inst* 93:39-45, 2001.
5. **Herbert B-S**, Wright WE, Shay JW. Telomerase and breast cancer. *Breast Cancer Research* 3:146-149, 2001.
6. Ramirez RD, Morales CP, **Herbert B-S**, Rohde J, Passons C, Shay JW, Wright WE. Putative telomere-independent mechanisms of replicative aging reflect inadequate growth conditions. *Genes and Development* 15:398-403, 2001.
7. Gryaznov S, Pongracz K, Matray T, Schultz R, Pruzan R, Aimi J, Chin A, Harley C, Shea-**Herbert B**, Shay J, Oshima Y, Asai A, Yamashita Y. Telomerase inhibitors- Oligonucleotide phosphoramidates as potential therapeutic agents. *Nucleosides, Nucleotides & Nucleic Acids* 20:401-410, 2001.
8. **Herbert B-S**, Pongracz K, Shay JW, Gryaznov SM. Oligonucleotide N3'→P5' phosphoramidates as efficient telomerase inhibitors. *Oncogene* 21:638-642, 2002.
9. **Herbert B-S**, Wright WE, Shay JW. p16^{INK4a} inactivation is not required to immortalize human mammary epithelial cells. *Oncogene* 21:7897-7900, 2002.
10. Ramirez RD, **Herbert B-S**, Vaughan MB, Zou Y, Gandia K, Morales CP, Shay JW. Bypass of telomere-dependent replicative senescence (M1) upon overexpression of Cdk4 in normal human epithelial cells. *Oncogene* 22:433-444, 2003.
11. **Herbert B-S***, Pearce VP, Hynan LS, LaRue DM, Wright WE, Kopelovich L, Shay JW. A peroxisome proliferator-activated receptor-gamma agonist and the p53-rescue drug CP-31398 inhibit the spontaneous immortalization of breast epithelial cells. *Cancer Research* 63:1914-1919, 2003. (*corresponding author)
12. Velicescu M, Yu J, **Herbert B-S**, Shay JW, Granada E, Dubeau L. Aneuploidy and telomere attrition are independent determinants of crisis in SV40-transformed epithelial cells. *Cancer Research* 63:5813-5820, 2003.
13. Pongracz K, Li S, **Herbert B-S**, Pruzan R, Wunder E, Chin A, Piatyszek M, Shay J, Gryaznov SM. Novel short oligonucleotide conjugates as inhibitors of human telomerase. *Nucleosides Nucleotides Nucleic Acids*: 22:1627-1629, 2003.

In rank:

14. Troester MA, Hoadley KA, Sørlie T, **Herbert B-S**, Shay J, Perou CM. Cell-type specific responses to chemotherapeutics in breast cancer. *Cancer Research* 64: 4218-4226, 2004.
15. Zhang H, **Herbert B-S**, Pan K-H, Shay JW, Cohen SN. Disparate effects of telomere attrition on gene expression during replicative senescence of human mammary epithelial cells cultured under different conditions. *Oncogene* 23:6193-6198, 2004.
16. Gilley D, Tanaka H, **Herbert B-S***. Telomere dysfunction in aging and cancer. *Intl J of Biochem and Cell Biol* 37:1000-1013, 2005. (*corresponding author)
17. **Herbert B-S***, Gellert G, Hochreiter A, Pongracz K, Wright WE, Zielinska D, Chin A, Harley CB, Shay JW, Gryaznov SM. Lipid modification of GRN163, an N3'→P5'- thio-phosphoramidate oligonucleotide, enhances the potency of telomerase inhibition. *Oncogene* 24:5262-5268, 2005. (*corresponding author).
18. Canales BK, Li Y, Thompson MG, Gleason JM, Chen Z, Malaeb B, Corey DR, **Herbert B-**

- S, Shay JW, Koeneman KS. Small molecule, oligonucleotide-based telomerase template inhibition in combination with cytolytic therapy in an in vitro androgen-independent prostate cancer model. *Urologic Oncology*, 24:141-51, 2006.
19. Hochreiter AE, Xiao H, Goldblatt EM, Gryaznov SM, Miller KD, Badve S, Sledge GW, **Herbert B-S**. The telomerase template antagonist GRN163L disrupts telomere maintenance, tumor growth and metastasis of breast cancer. *Clinical Cancer Research* 12: 3184-3192, 2006.
 20. Lewis C*, **Herbert B-S*** (*co-first author), Bu D, Halloway S, Beck A, Shadeo A, Ashfaq R, Brekken R, Lam W, Shay JW, Euhus D. Telomerase immortalization of human mammary epithelial cells derived from a *BRCA2* mutation carrier. *Breast Cancer Research and Treatment* 99:103-115, 2006.
 21. **Herbert B-S***, Hochreiter AE, Wright WE, Shay JW. Non-radioactive detection of telomerase activity using the Telomeric Repeat Amplification Protocol (TRAP). *Nature Protocols* 1: 1583-1590, 2006 (*corresponding author).
 22. Malkas LH, **Herbert B-S**, Abdel-Aziz W, Dobrolietcki L, Liu Y, Alagharu S, Beamon A, Hoelz D, Badve S, Schnaper L, Arnold R, Mechref Y, Novotny MV, Loehrer P, Goulet R, Hickey R J. A cancer-associated PCNA expressed in breast cancer has implications as a potential biomarker. *Proc Natl Acad Sci USA* 103: 19472-19477, 2006.
 23. Gomez-Millan J, Goldblatt EM, Gryaznov S, Mendonca MS, **Herbert B-S**. Specific telomere dysfunction induced by GRN163L increases radiation sensitivity in breast cancer cells. *International Journal of Radiation Oncology, Biology, Physics* 67: 897-905, 2007.
 24. Gryaznov SM, Jackson S, Dikmen G, Harley C, **Herbert BS**, Wright WE, Shay JW. Oligonucleotide conjugate GRN163L targeting human telomerase as potential anticancer and antimetastatic agent. *Nucleosides Nucleotides Nucleic Acids* 26:1577-1579, 2007.
 25. Huda N, Tanaka H, **Herbert B-S**, Reed T, Gilley D. Shared environmental factors associated with telomere length maintenance in elderly male twins. *Aging Cell* 6:709-713, 2007.
 26. Gilley D, **Herbert B-S**, Tanaka H, Huda, N, Reed T. Factors impacting human telomere homeostasis and age-related disease. *Mechanisms of Aging and Development*, 129: 27-34, 2008.
 27. Zhang Y, **Herbert B-S**, Gentry ER, Rajashekhar G, Clauss M, Ingram D, Yoder M, Rehman J. Premature Senescence of Cord-blood Derived Endothelial Progenitor Cells Induced by Tumor Necrosis Factor-alpha and Oxidative Stress. Submitted.
 28. Goldblatt EM, Erickson PA, Gentry ER, Gryaznov SM, **Herbert B-S**. Lipid-conjugated telomerase antagonists sensitize HER2+ and resistant breast cancer cells to trastuzumab. Submitted.

Book chapters and reviews (non-refereed):

1. **Herbert B-S**, Shay JW, Wright WE. Chapter 18: Analysis of telomeres and telomerase. In *Current Protocols in Cell Biology*. John Wiley & Sons, Inc., New York, NY, p18.6.6, 2003.

In rank:

2. **Herbert B-S**. Advances in breast cancer therapy and chemoprevention: current strategies and new approaches. *Cancer Therapy* 1 (December): 363-371, 2003.
3. Malkas LH, Hoelz D, Abdel-Aziz W, **Herbert B-S**, Schnaper L, Hickey RJ. A functional proteomic approach for biomarker discovery. *Drug Discovery and Development*, Aug 2006 issue online.

4. **Herbert B-S**, Goldblatt EM. Therapeutic targets and drugs- Telomerase: Telomerase inhibitors including telomerase associated protein inhibitors. In *Cancer Drug Discovery and Development: Telomeres and Telomerase in Cancer*. Humana Press, Springer Science and Business Media, New York, NY, 2008.

Published Abstracts (refereed):

1. **Herbert B-S**, Perou CM, Wright WE, Kopelovich L, Shay JW. Effects of chemopreventive agents on the spontaneous immortalization of breast epithelial cells from individuals predisposed to breast cancer. *Cancer Epidemiology, Biomarkers, & Prevention* 11 (10): 1157S- A220, 2002.

In rank:

2. Karpf DB, Gryaznov SM, Chin AC, Go NF, Lam Q, Nazzal D, Pongracz K, Pruzan R, Shay J, **Herbert B-S**, Wright WE, Trager J, Wunder E, Yonker M, Zielinska D, Harley CB. GRN719, an optimized telomerase inhibitor for the treatment of cancer: In vitro and in vivo activity, PK/PD, and in vivo safety. *Clinical Cancer Research* 9 (16): 6256S-6256S, 2003.
3. **Herbert B-S**, Wandinger-Ness A, Bacallao R. A renal epithelial autosomal dominant polycystic kidney disease cell line immortalized with telomerase. *Journal of the American Society of Nephrology* 16 (S3): 120, 2005.
4. **Herbert B-S**, Hochreiter A, Pongracz K, Gryaznov SM. Effects of the potent telomerase antagonist GRN163L in breast cancer. *Breast Cancer Research and Treatment* 94 (S1): 1076, 2005.
5. Clare SE, Kolanko P, Blosser R, Xiao H, Badve S, **Herbert B**. Non-transformed basal (cytokeratin 5/14 positive) breast cells migrate in Matrigel by collective cell migration. *Breast Cancer Research and Treatment* 94 (S1): 6111, 2005.
6. Agarwal B, **Herbert B-S**, Schnaper L, Liu Y, Dobroliedki LE, Hoelz D, Hickey RJ, Malkas LH. A Cancer-Specific Isoform of PCNA is Linked to Breast Cancer: Implications for a Novel Cancer Biomarker. *Archives of Pathology & Laboratory Medicine* 130: 1397, 2006.
7. Malkas LH, **Herbert B-S**, Hoelz D, Abdel-Aziz W, Schnaper L, Dobroliedki L, Liu Y, Alagharu S, Badve S, Beamon A, Arnold R, Mechref Y, Novotny MV, Loehrer P, Hickey RJ. A cancer-specific isoform of PCNA is linked to breast malignancy: implications for a novel biomarker. *Breast Cancer Research and Treatment* 95 (S1): 1018, 2006.
8. Gomez-Millan J, Goldblatt E, Gryaznov S, Mendonca MS, **Herbert B-S**. Specific telomere dysfunction induced by GRN163L increases radiation sensitivity in breast cancer cells. *International Journal of Radiation Oncology, Biology, Physics* 66 (S1): S559-S560, 2007.
9. Hickey RJ, **Herbert B-S**, Agarwal B, Dobroliedki LE, Malkas LH, Schnaper L, Liu Y, Hoelz D. A cancer-specific isoform of PCNA is linked to breast cancer: implications for a novel cancer biomarker. *Laboratory Investigation* 87: 307A, 2007.
10. Hickey RJ, **Herbert B-S**, Agarwal B, Dobroliedki LE, Malkas LH, Schnaper L, Liu Y, Hoelz D. A cancer-specific isoform of PCNA is linked to breast cancer: implications for a novel cancer biomarker. *Modern Pathology* 20: 1415, 2007.
11. Mangum C, Cameron J, and **Herbert B-S**. Effects of resveratrol on triple negative (ER-, PR-, HER2-) breast cancer cells. *FASEB J* 22: 898.45, 2008.

Research Conference Abstracts/Presentations (all while in rank; # indicates oral presentation):

1. **Herbert B-S**, Pongracz K, Harley C, Shay JW, Gryaznov S. (2003) Modified thio-

- phosphoramidates as effective telomerase inhibitors. *Cold Spring Harbor Meeting on Telomeres and Telomerase*.
2. # **Herbert B-S.** (2003) Bypass of telomere-dependent replicative senescence (M1). *43rd American Society for Cell Biology Annual Meeting* (platform presentation).
 3. Gellert GC, Dikmen ZG, **Herbert B-S**, DeBrabander JK, Shay JW. (2004) Effects of a Novel Vacuolar-ATPase Inhibitor as a Potential Chemotherapeutic Agent. *Lung Cancer Investigators' Meeting, San Diego, CA*.
 4. **Herbert B-S**, Hochreiter A, Gellert GC, Larue D, Pongracz K, Wright WE, Harley C, Shay J W, Gryaznov SM. (2004) Lipid Modification of Oligonucleotide N3' → P5' – thio-Phosphoramidates Complementary to hTR Template Region Enhances the Efficacy of Telomerase Inhibition. *AACR Special Conference on "The Role of Telomeres and Telomerase in Cancer."*
 5. **Herbert B-S**, Lewis C, Shay JW, Euhus D. (2004) Establishment of an Immortalized Breast Epithelial Cell Line Derived from a Germ-line *BRCA2* Mutation Carrier. *AACR Special Conference on "The Role of Telomeres and Telomerase in Cancer."*
 6. #Zhang H, **Herbert B-S**, Pan K-H, Shay JW, Cohen SN. (2004) Disparate effects of telomere attrition on gene expression in different cell lineages and culture conditions indicate heterogeneity of the senescence process. Oral presentation: *AACR Special Conference on "The Role of Telomeres and Telomerase in Cancer."*
 7. Hochreiter A, **Herbert B-S**. (2005) Cell-type specific responses to telomerase inhibition in breast cancer. *7th Annual Amelia Project Meeting (Indianapolis, In)*.
 8. **Herbert B-S**, Hochreiter A, Gryaznov SM. (2005) Consequences of telomerase inhibition by GRN163L in breast cancer cells. *96th Annual AACR Meeting*.
 9. Lewis C, **Herbert B-S**, Bu D, Holloway S, Beck A, Ashfaq R, Shay JW, Euhus D. (2005) Establishment and characterization of a breast epithelial cell line derived from a germ-line *BRCA2* mutation carrier. *96th Annual AACR Meeting*.
 10. Hoelz DJ, **Herbert B-S**, Schnaper L, Arnold R, Dobroliiecki L, Liu Y, Liu J, Badve S, Hickey RJ, Malkas LH. (2005) Cancer specific proliferating cell nuclear antigen as a novel diagnostic marker for the detection of breast cancer. *DOD Era of Hope Meeting*.
 11. Zhang Q, Kao C, Vieth E, **Herbert B-S**, Jeng M-H. (2006) CARM1 Stimulates hTERT Transcription and Telomerase Activity. *Keystone Nuclear Receptor Meeting*.
 12. Goldblatt E, Hochreiter A, Xiao H, **Herbert B-S**. (2006) Effects of Telomerase Inhibition in MDA-MB-231 Breast Cancer Cells. *6th Annual Amelia Project Meeting; IUSCC Cancer Research Day (Indianapolis, In)*.
 13. # Gomez-Millan J, Goldblatt E, Gryaznov S, Mendonca MS, **Herbert B-S**. (2006) Specific telomere dysfunction induced by GRN163L increases radiation sensitivity in breast cancer cells. *8th Annual Midwest DNA Repair Symposium (Indianapolis, In)*. Oral presentation
 14. Gomez-Millan J, Goldblatt E, Gryaznov S, Mendonca MS, **Herbert B-S**. (2006) Specific telomere dysfunction induced by GRN163L increases radiation sensitivity in breast cancer cells. *American Society for Therapeutic Radiology and Oncology 48th Annual Meeting (Philadelphia, PA)*.
 15. Agarwal B, **Herbert B-S**, Schnaper L, Liu Y, Dobroliiecki LE, Hoelz D, Hickey RJ, Malkas LH. (2006) A Cancer-Specific Isoform of PCNA is Linked to Breast Cancer: Implications for a Novel Cancer Biomarker. *(CAP'06-The Pathologist's Meeting)*.
 16. Kher R, Xu W-M, Ward HH, **Herbert B-S**, Wandinger-Ness A, Bacallao RL. (2006) Alterations in Wnt/wg Gene Signaling in Cell Lines with Mutations in Polycystin-1.

- American Society for Cell Biology Annual Meeting.*
17. Gomez-Millan J, Goldblatt EM, Gryaznov SM, Mendonca MS, and **Herbert B-S.** (2006) Specific Telomere Dysfunction Induced by GRN163L Increases Radiation Sensitivity of Breast Cancer Cells. *Translational research in Radiation Oncology symposium.*
 18. Goldblatt E, Hochreiter A, **Herbert B-S.** (2006) Effects of Telomerase Inhibition in MDA-MB-231 Breast Cancer Cells. *ACS Greater Midwest Conference* (Grand Rapids, MI).
 19. Gryaznov SM, Jackson S, Dikmen G, Harley C, **Herbert B-S,** Wright WE, Shay JW. (2006) Oligonucleotide Conjugate GRN163L Targeting Human Telomerase as Potential Anticancer and Antimetastatic Agent. *Oligo, Nucleosides and Nucleotides Meeting* (Bern, Switzerland).
 20. Malkas LH, **Herbert B-S,** Hoelz D, Abdel-Aziz W, Schnaper L, Dobroliiecki L, Liu Y, Alagharu S, Badve S, Beamon A, Arnold R, Mechref Y, Novotny MV, Loehrer P, Hickey R J. (2007) A cancer-specific isoform of PCNA is linked to breast malignancy: implications for a novel biomarker. *100th Annual AACR Meeting.*
 21. Huda N, Tanaka H, **Herbert B-S,** Reed T, and Gilley D. (2007) Non-genetic factors associated with telomere maintenance in elderly male twins. *Cold Spring Harbor Meeting on Telomeres and Telomerase.*
 22. Goldblatt E, Hochreiter A, Stanton K, Clare S, Miller K, and **Herbert B-S.** (2007) Anti-tumorigenic Effects of the Novel Telomerase Inhibitor GRN163L in Breast Cancer Cells. *IU Simon Cancer Center Cancer Research Day Scientific Poster Session. *Best poster award for a graduate student.*
 23. Malkas LH, Schnaper L, **Herbert B-S,** Abdel-Aziz W, Liu Y, Dobroliiecki L, Hoelz D, Aggarwal S, Badve S, Goulet R, Hickey RJ. (2007) Expression of a cancer associated isoform of PCNA in breast cancer has implications as a potential biomarker. *American Society of Clinical Oncology (ASCO).*
 24. Ositelu O, Goldblatt E, and **Herbert B-S.** (2007) The Anti-Adhesive Effects of GRN163L Sensitize Breast Cancer Cells to Paclitaxel. *IUSCC Summer Research Program Symposium.*
 25. Mangum C, Cameron J, and **Herbert B-S.** (2007) Effects of resveratrol on triple negative (ER-, PR-, HER2-) breast cancer cells. *IUPUI Summer Research Opportunities Symposium* (Indianapolis, IN); *Annual Biomedical Research conference for Minority Students* (Austin, TX).
 26. Goldblatt E, Ositelu O, Gryaznov S, Tressler S, and **Herbert B-S.** (2007) The effects of GRN163L and sensitization of breast cancer cells to paclitaxel. *AACR Special Conference on "The Role of Telomeres and Telomerase in Cancer."*
 27. Martin JC, **Herbert B-S,** and Hocevar BA. (2008) Regulation of epithelial-to-mesenchymal transition by Disabled-2. *Keystone Transforming Growth Factor-Beta Meeting.*
 28. Zhang Y, **Herbert B-S,** Gentry ER, Rajashekhar G, Clauss M, Ingram D, Yoder M, Rehman J. (2008) Premature Senescence of Cord-blood Derived Endothelial Progenitor Cells Induced by Tumor Necrosis Factor-alpha via the P38 MAPK Pathway. *Keystone Cell Death and Cellular Senescence (J8) Meeting.*
 29. Mangum C, Cameron J, and **Herbert B-S.** (2008) Effects of resveratrol on triple negative (ER-, PR-, HER2-) breast cancer cells. *Mississippi Academy of Sciences Conference; Federation of American Societies for Experimental Biology Meeting* (San Diego, CA). ***Third place oral presentation/ abstract award for a graduate student.**
 30. **Herbert B-S,** Goldblatt EM, Erickson PA, Gentry ER, Gryaznov SG. (2008) Lipid-conjugated telomerase antagonists sensitize HER2+ and resistant breast cancer cells to trastuzumab. *2008 AACR Annual Meeting, San Diego (Late-breaking abstract).*

31. Smith CB, Gentry ER, Goldblatt EM, **Herbert B-S.** (2008). Investigation of breast cancer cell inhibition using p53 stabilizing drugs CP-31398 and PRIMA-1 in cells derived from patients with Li-Fraumeni Syndrome. *IU Simon Cancer Center Cancer Research Day Scientific Poster Session. (Indianapolis, IN).*
32. # **Herbert B-S.** (2008) Targeting Telomerase and Senescence Mechanisms in Breast Tumor-Initiating Cells. *British Association for Cancer Research Conference on Cellular Immortality & Cancer: From Telomerase to Cancer Stem Cells (Stratford upon Avon, UK).* Oral presentation.

III. PROFESSIONAL SERVICE: None

IV. INTEGRATION OF TWO OR MORE ASPECTS OF FACULTY WORK: None

7/7/08
(Date)



(Signature of Candidate)